



IJPPR

INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH  
An official Publication of Human Journals

ISSN 2349-7203





Human Journals

Review Article

January 2018 Vol.:11, Issue:2

© All rights are reserved by Darshani Sonavaria et al.

## A Review of Probable Mechanism of Action of Herbal Sleep Inducing Formulation- Sleecap

	
<b>Darshani Sonavaria<sup>*</sup>, Dr. Chetna Chotalia, Kavita Salkar, Rajiv Salvi</b>	
<i>Piramal Phytocare Limited, Light Hall - A wing, Saki Vihar Road, Chandivali, Andheri - (E), Mumbai-400 072, Maharashtra, India.</i>	
<b>Submission:</b> 27 December 2017	
<b>Accepted:</b> 3 January 2018	
<b>Published:</b> 30 January 2018	



[www.ijppr.humanjournals.com](http://www.ijppr.humanjournals.com)

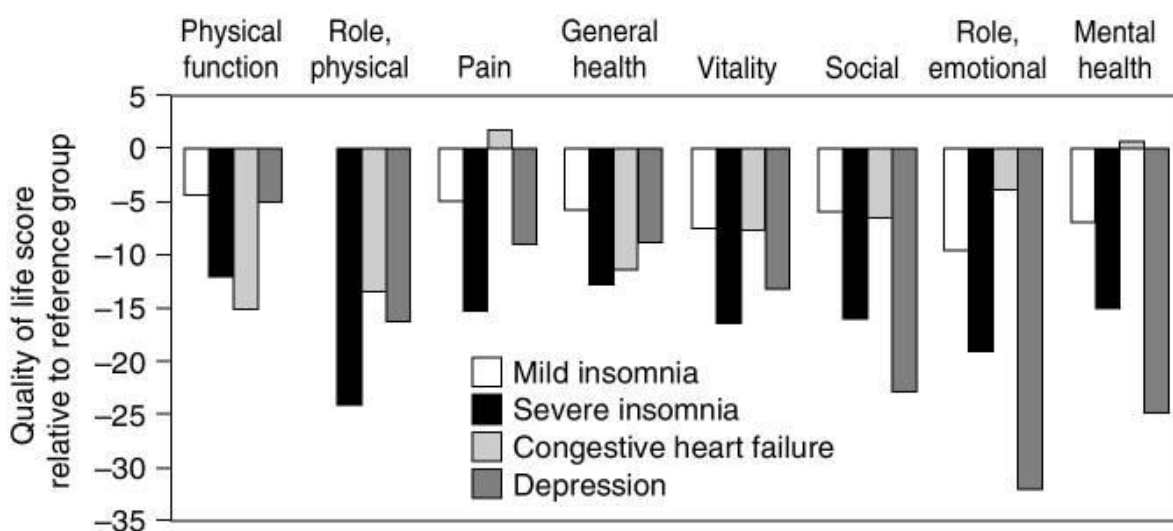
**Keywords:** Insomnia, Natural Tranquilizer, Herbal Sleep Inducer, Phytoformulation, Sleecap

### ABSTRACT

Insomnia is a common sleep arising disorder from conditions like stress, anxiety, depression, changes in modern lifestyle including several medications, lack of exercise, jet lag. To review possible mechanism of action of herbal sleep inducing formulation. Herbal formulation containing unique constituents like *Convolvulus pluricaulis*, *Nardostachys jatamansi*, *Withania somnifera* and *Rauwolfia serpentine* induces sleep naturally by rejuvenating the nervous system, removes insomnia and eases stress. These ingredients altogether can act as natural tranquilizer, sedative, brain tonic, have anxiolytic effect, anti-stress, anti-depressant, hypotensive action, anti-oxidant, adaptogenic and neuroprotective effects. A product with multi ingredient, each with a different activity profile would be an ideal product for sleep-disorder rather than a single ingredient product which is recommended in combination resulting in synergistic effect. This natural herbal insomnia formulation is safe and efficacious for insomnia.

## INTRODUCTION

Sleep is a behavioral state which is a natural and crucial part of every individual's life. Lack of good sleep or interrupted sleep can weaken immune system and can cause other serious ailments. Sleep is crucially important in the animal kingdom. Sleep disorders affect a large portion of the population worldwide and insomnia is the most commonly reported sleep disorder. Prevalence of insomnia increases with age, this problem is potentially increasing in elderly population<sup>1</sup>. Sleep loss and sleep disorders affect an individual's performance, safety, and quality of life. Almost 20 percent of all serious car crash injuries in the general population are associated with driver sleepiness, independent of alcohol effects<sup>2</sup>. Compared to healthy individuals, individuals suffering from sleep loss, sleep disorders, or both are less productive, have an increased health care utilization, and an increased likelihood of accidents.



The available products for sleep disorders are present with various side-effects like sedation, muscle relaxation, amnesia, and dependence.

Sleecap is a unique combination of four effective plant-based ingredients like *Convolvulus pluricaulis*, *Nardostachys jatamansi*, *Withania somnifera* and *Rauwolfia serpentine*.

Sleecap is a product of Piramal Phytocare Limited, India.

Various chemical constituents from these plants are isolated and studied for their pharmacological effects. The product is duly studied for its efficacy and safety in sleep

disorder patients. “Sleecap” significantly delayed the onset of fatigue and reduced the number of errors among individuals.

A marked relaxation of the occipitofrontalis muscle was noticed after three months of therapy. The continuous oral administration of “Sleecap” for three months did not show any neurological, psychiatric or endocrinal side-effects. Neither any harmful effect upon the body, nor any dependence, or any withdrawal symptoms were observed with Sleecap.

### **Mode of action:**

Sleecap can be presented as an effective option for insomnia. It does not act as a sedative and its rejuvenative and nervine properties help the body to settle and sleep. It helps the body to address a stress related condition rather than masking it with sedatives. Sleecap rejuvenates the nervous system, erases insomnia and eases stress.

Sleecap is formulated using well known plants documented for their proved actions in a scientific way. The plant extracts present in the product are - *Convolvulus pluricaulis*, *Nardostachys jatamansi*, *Withania somnifera* and *Rauwolfia serpentine*.

### **Different pharmacological activities:**

#### **1. Tranquilizing action and sedative action:**

The compounds shankpushpi, convolamine, jatamansone and jatamansin<sup>3</sup> help brain to calm down and relieve the tension, and thus act as tranquilizer. They induce feeling of calm and peace, good sleep and gives relief in mental fatigue. The product acts as a brain tonic and helps in treating mental retardation and mental disorders.

#### **The compounds act in following way:**

- Induces and increases sleeping time (as studied in animals which received 1 month dosing of this extract)<sup>4</sup>
- reduces spontaneous motor activity<sup>5</sup>
- Reduces epinephrine content which is increased in sleeping disorders<sup>6</sup>

- induces hypothermia<sup>7</sup>
- reduction in exploratory behavioral pattern, and suppression of aggressive behaviour<sup>8</sup>
- Balances the levels of norepinephrine (NE), dopamine (DA), serotonin (5-HT), 5-hydroxyindoleacetic acid (5-HIAA), gamma-aminobutyric acid (GABA)<sup>1</sup>
- Jatamansone reduces the aggressiveness, stubbornness, restlessness and insomnia<sup>9</sup>
- Furthermore, these compounds show fewer side effects as compared to D-amphetamine and chlorpromazine, the commonly used sedatives

These findings explicitly suggest that the compounds possess a potential CNS-depressant activity.

## 2. Anti-anxiety action (Anxiolytic effect<sup>10</sup>):

Anxiety is one of the major predisposing factors for sleep disturbance. The various compounds shankhpushp<sup>11</sup>, scopoletin, resperine and withaferin A and withanolide D present in the product controls anxiety through their anxiolytic effect and thus regulates the sleep pattern.

- Various pharmacological studies indicated the anxiolytic like effect of compounds and further, the results were quite comparable to diazepam (1 mg/kg) which is the standard anxiolytic drug.
- The compounds shankhpushpi and scopoletin kaempferol, withaferin A and withanolide D have GABA-mimetic activity. They act as GABA-A agonists and reduces the activity in the brain cells and thus attribute to the CNS depressant effect.
- The active compounds modify the phenomenon of GABA system at the level of the synthesis of GABA mediators, release or reuptake or metabolism. The probable mechanism through GABA-A receptors<sup>12</sup> which are the most abundant inhibitory receptor system in the CNS and binding of an agonist to its recognition site results in increased chloride ion flux which in turn hyperpolarizes the postsynaptic membrane.

➤ The compounds also reduce the neuromuscular coordination indicative of the muscle relaxant activity.

➤ The observed effects were comparable to the reference drug of Diazepam.

### 3. Anti-stress action:

➤ Shankhpushpine<sup>13</sup> and convolamine control the production of body's stress hormones like adrenaline and cortisol in our body and help in reducing stress.

➤ Jatamansone and jatamansin show potent antioxidant activity and reduce the stress-induced elevation of lipid peroxidation and nitric oxide levels and decrease in catalase activity in the brain. The compounds have a regulatory action on adrenal gland and also controls the corticosterone levels in plasma. Thus, the compounds show potent anti-stress activity which is due to its antioxidant activity.

➤ The compounds- withaferin A and withanolide D have a GABA-mimetic activity contributing to anti-stress activity.

### 4. Anti-depression action:

The various compounds present in the product have anti-depression activity through different mechanisms and thus controls the negative effect on sleep induction.

➤ The compounds shankhpushpine<sup>14</sup>, convolamine, scopoletin and kaempferol elicit a significant antidepressant like effect in mice by interaction with the adrenergic, dopaminergic, and serotonergic systems. They increase the levels of norepinephrine, dopamine and serotonin in brains of mice. They also reduce the level of plasma cortisol, high levels of cortisol are associated with depressed mood in humans.

➤ Jatamansone<sup>15</sup> and jatamansin<sup>16</sup> and withanolide D increases the levels of central monoamines and inhibitory amino acids, including a change in the levels of serotonin, 5-hydroxyindole acetic acid, GABA, and taurine and increases the levels of catecholamines and indoleamines and thus contribute to the anti depression activity.

➤ The activity was comparable to anti-depressant drug imipramine and the anti-anxiety drug lorazepam.

### **5. Neuroprotective action:**

Neurodegeneration with age and disease related (Alzheimer's and Parkinson's disease) causes a negative impact on sleep patterns in elderly.

Various neuroprotective compounds cause neuroprotective interventions and help to induce natural sleep in these elderly population.

➤ Withaferin A and withanolide D<sup>17</sup> prevents neural damage to the cortex, hippocampus and spinal cord and reduces the number of degenerating cells in brain.

➤ Resperine<sup>11</sup> helps to treat central nervous system disorders. It causes depletion of catecholamines at the central and peripheral level and depletion of Serotonin at the central level.

➤ Jatamansone and Jatamansin<sup>18</sup> act as neuroprotective agent by inhibition of Acetylcholine. The protective effect may be associated with improving glutathione content, inhibiting lipid peroxidation, and activity on the Na<sup>+</sup>/K<sup>+</sup> ATPase and catalase enzyme systems.

➤ Shankhpushpine<sup>19</sup>, convolamine and scopoletin are useful to treat neurodegenerative diseases and also used to treat nervous debility. They reduce neurotoxicity, enhancing activity through anti-Acetylcholine effect.

### **6. Antioxidant action<sup>20,21</sup>:**

Antioxidants are involved in the prevention of cellular damage.

All the four ingredients have potent antioxidants actions, which correct and prevent the free radical-induced oxidative damage to various organs and systems. The compounds provide protection against lipid peroxidation.

## 7. Adaptogenic action:

Adaptogens help to adopt changes in life and environment and increase stamina and overall performance. Adaptogens are the drugs of choice to treat stress and fatigue.

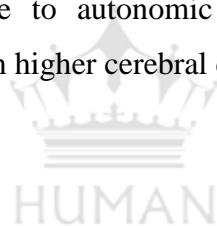
Withanolides from *Withania somnifera*<sup>22</sup> promote the growth of axons and dendrites.

## 8. Hypotensive action:

Reserpine and other alkaloids from the root of *Rauwolfia serpentina*<sup>23</sup> have a sympatholytic effect by releasing noradrenaline and inhibiting its resorption in the vesicles of the noradrenergic nerve ends. This results in a lowering of catecholamine, which causes a hypotensive effect. Reserpine<sup>24</sup> diminishes reflex vasomotor responses but also has a direct effect on the peripheral vessels independent of its nervous activity.

The compounds shankpushpine<sup>25</sup> and convolamine also shows hypotensive effect. Hypotensive effect was mainly due to autonomic ganglion blocking action and was augmented by the depressant action on higher cerebral centers.

## Comparison with competitors



### 1. A multi-ingredient product V/S single ingredient products

Sleep disorder is a multifactorial disorder. Various factors with different pharmacologies like stress, depression and anxiety contribute to sleeplessness. Hence, a product with multi ingredient, each with a different activity profile would be an ideal product for sleep-disorder.

The single ingredient products like Valerian which works on the nerve channels and helps in rejuvenation are being used for sleep-disorders, however, it is recommended to use it in combination as it is also known to have a dulling effect.

### 2. Comparison with other plant products

Valeriana (Tagar) which is used in sleep disorders was compared with one of the ingredient of our product –Jatamansi<sup>26</sup>. The clinical study showed that same effect was observed in both the groups in terms of symptoms such as sleep initiation, duration of sleep, and disturbed sleep.

However, the product Sleecap is present with the additional beneficial effects of other three ingredients as well.

### 3. Efficacy comparable to standard drugs in use

The compounds present in the product Sleecap shows comparable efficacy to some of the well-known drugs used in stress and anxiety.

- The anti-depressant activity of *Convolvulus pluricaulis*<sup>27</sup> was found to be comparable to that of imipramine and fluoxetine administered for 10 successive days.
- *Convolvulus pluricaulis* anxiolytic like effect of drug was quite comparable to diazepam (2mg/kg) which is the standard anxiolytic drug.
- *Nardostachys jatamansi* extract showed anxiolytic effects comparable to the positive control i.e., diazepam.
- Antidepressant effects of *Nardostachys jatamansi* were comparable with imipramine and the anti-anxiety drug lorazepam.
- Comparative studies against D-amphetamine, chlorpromazine showed that Jatamansone reduced the aggressiveness, stubbornness, restlessness and insomnia.

### 4. Safety vs. standard drugs

Benzodiazepines are the most preferred treatment, but these compounds have well known side-effects such as sedation, muscle relaxation, amnesia and dependence.

The product Sleecap does not show these side-effects. The various studies show that the ingredients present in the product showed comparable efficacy to some of the well known drugs, however, were free from or showed fewer side effects as compared to D-amphetamine and chlorpromazine, imipramine, lorazepam etc.



## 5. Safety vs. other plant based products

Some of the plant based products used for sleep-disorders have activity same as of the Sleecap product's individual ingredient's activity, although they were present with some side-effects.

Like *Withania* extract was about the same as the activity of the ginseng extract; however, *Panax ginseng* results in ginseng-abuse syndrome, a condition characterized by high blood pressure, water retention, muscle tension and insomnia

Similarly, melatonin has shown effect on testosterone levels in males and hence comes with a caution.

## 6. Side Effects of the Pharmacological/ Allopathic Therapies –

Some of the common side-effects observed with this therapy are listed below:

Dizziness, drowsiness, somnolence, fatigue, body imbalance, loss of memory, difficulty in carrying out voluntary movements, dry mouth, impaired coordination, drugs dependence and withdrawal symptoms.

## CONCLUSION:

It is therefore concluded that Sleecap is a natural herbal product with multiple ingredients, each having different activity profile mentioned in below chart. It would be an ideal product for sleep-disorder which is safe and efficacious for insomnia.

Name of the Herbal extract	Actions	Activity Profile
<b>Shankpushpi</b> ( <i>Convolvulus pluricaulis</i> )	Relieves anxiety and mental fatigue	Acts on acetylcholine content, Controls stress hormones like adrenaline and cortisol
<b>Sarpagandha</b> ( <i>Rauwolfia serpentina</i> )	Improves sleep	Depletes neuronal storage granules of serotonin and norepinephrine dopamine <i>Serpentina</i> causes marked inhibition of succinate hydrogenase in brain
<b>Jatamansi</b> ( <i>Nardostachys jatamansi</i> )	Controls stress, insomnia and tension	Inhibits acetylcholine activity and change in levels of serotonin
<b>Ashwagandha</b> ( <i>Withania somnifera</i> )	Relieves stress, Stabilizes mood	Helps promote sleep by involving GABAergic modulation which imparts anxiolytic activity and nervous system tonic effects

## REFERENCES:

1. Yuan Shi: Current Neuropharmacology; Herbal Insomnia Medications that Target GABAergic Systems: A Review of the Psychopharmacological Evidence, 2014, 12, 289 -302
2. 5% Indians suffering from sleep disorders: Study, Kounteya Sinha | TNN | Aug 3, 2012,
3. R.B. Arora, M. Singh and Chandra Kanta, Tranquilizing Activity of Jatamansone - A Sesquiterpene From *Nardostachys jatamansi*, Life Sciences No. 6, pp. 225-228, 1962
4. Bone Kerry, Mills Simon Principles and Practice of Phytotherapy. 2<sup>nd</sup> edn; Part III, Pg 848
5. S Timothy, Tracy and Richard L. Kingston, Herbal Products Toxicology and Clinical Pharmacology. 2<sup>nd</sup> edn, 59.
6. Nilesh Shah, Abha Bang, and Aparna Bhagat, Indian research on sleep disorders, Indian J Psychiatry. 2010 Jan; 52(Suppl1): S255–S259.
7. JF Pagel, BL Parnes, Medication for the treatment of sleep disorders: an overview, J Clin Psychiatry, 2001; 3(3).
8. Narvaes, R., & Martins de Almeida, R. M. (2014). Aggressive behavior and three neurotransmitters: dopamine, GABA, and serotonin—A review of the last 10 years. *Psychology & Neuroscience*, 7(4), 601-607
9. Sakina Razack and Farhath Khanum, Anxiolytic effects of *Nardostachys jatamansi* DC in mice, Annals of Phytomedicine 2012;1(2): 67-73,
10. Ashfaq Ahmad, Munavvar Z. A. Sattar, Hassaan A. Rathore, Tabinda Fatima, Safia Akhtar Khan et al, Pharmacological importance of *Nardostachys jatamansi* DC: A potential therapeutic agent in different pathological ailments, Journal of Chemical and Pharmaceutical Research, 2013; 5(10):431-438
11. K. Sharma, V. Arora, A. C. Rana and M. Bhatnagar, Anxiolytic effect of *Convolvulus pluricaulis choisy* Petals on elevated plus maze model of anxiety in mice, Journal of Herbal Medicine and Toxicology 2009;3 (1) 41-46.
12. Mehta AK, Binkley P, Gandhi SS, Ticku MK., Pharmacological effects of *Withania somnifera* root extract on GABA A receptor complex, Indian J Med Res. 1991 ;94:3125.
13. Neeraj.K. Sethiy, Sangeeta. G. Thakore and S.H. Mishra, Comparative evaluation of commercial sources of indigenous Medicine Shankhpushpi for anti-stress potential, A preliminary study, Pharmacologyonline 2009;2: 460-467.
14. Dinesh Dhingra and Rekha Valecha, Screening for antidepressant-like activity of *Convolvulus pluricaulis choisy* in mice, *Pharmacologyonline*1: 2007;262-278.
15. Purnima, Meenakshi Bhatt and Preeti Kothiyal, A review article on phytochemistry and pharmacological profiles of *Nardostachys jatamansi* DC-medicinal herb, Journal of Pharmacognosy and Phytochemistry 2015; 3(5): 102-106
16. Amritpal Singh, Anil Kumar, Sanjiv Duggal, *Nardostachys jatamansi* dc. Potential herb with CNS effects, JPRHC 2009;1(2). 276-290
17. Mohammad Hossein Mirjalili, Elisabeth Moyano, Mercedes Bonfill, Rosa M. Cusido and Javier Palazón, Steroidal Lactones from *Withania somnifera*, an Ancient Plant for Novel Medicine, *Molecules* 2009;14, 2373-2393.
18. Reeta Kumaria, Brijesh Rathib, Anita Ranic, Sonal Bhatnagar, *Rauvolfia serpentina* L. Benth. ex Kurz.: Phytochemical, Pharmacological and Therapeutic Aspects Int. J. Pharm. Sci. Rev. Res., 2013;23(2);, n° 56, 348-355
19. Hetal Amin, Rohit Sharma, Mahesh Vyas, P. K. Prajapati, Kartar Dhiman, *Shankhpushpi (Convolvulus pluricaulis Choisy)*: Validation of the Ayurvedic therapeutic claims through contemporary studies, International Journal of Green Pharmacy | October-December 2014 |
20. Sristi Verma, Reema Sinha, Puspendra Kumar, Faizal Amin, Jainendra Jain and Shivani Tanwar, Study of *Convolvulus pluricaulis* for Antioxidant and Anticonvulsant Activity, *Central Nervous System Agents in Medicinal Chemistry*, 2012;12, 55-59
21. Nazmun Lyle et al, Stress modulating antioxidant effect of *Nardostachys jatamansi* , Indian j of Biochemistry and Biophysics, 2009;46, 93-98
22. Qamar Uddin, L. Samiulla, V. K. Singh and S. S. Jamil, Phytochemical and Pharmacological Profile of *Withania somnifera* Dunal: A Review, Journal of Applied Pharmaceutical Science 02 (01); 2012: 170-175

23. Payal Rathi, Reeta Kumari, Chatrasal S Rajput and SS. Sawhney Therapeutic Characteristics of Rauwolfia Serpentina, International Journal Of Pharmaceutical And Chemical Sciences, 2013; 2 (2).
24. Gawade B.V. and Fegade S.A, Rauwolfia (Reserpine) As a Potential Antihypertensive Agent: A Review, *Int.J.Pharm. Phytopharmacol. Res.* 2012; 2(1): 46-49.
25. Debjit Bhowmik, K.P. Sampath Kumar, Shravan Paswan, Shweta Srivatava, Akhilesh Yadav, Amitsankar Dutta, Traditional Indian Herbs *Convolvulus pluricaulis* and Its Medicinal Importance, Journal of Pharmacognosy and Phytochemistry 2012; 1 (1 )
26. E. Toolika, Narayana Prakash Bhat, and Suhas Kumar Shetty. A comparative clinical study on the effect of Tagara (*Valeriana wallichii* DC.) and Jatamansi (*Nardostachys jatamansi* DC.) in the management of Anidra (primary insomnia), *Ayu.* 2015 ;36(1): 46–49
27. Parul Agarwal, Bhawna Sharma, Amreen Fatima, Sanjay Kumar Jain, An update on Ayurvedic herb *Convolvulus pluricaulis* Choisy, *Asian Pac J Trop Biomed* 2014; 4(3): 245-252

